Biochimica et Biophysica Acta 1787 (2009) 1289–1290

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbabio

Preface

# Mitochondrial calcium in health and disease

Interest in mitochondria has experienced a renaissance in the last 10–20 years. A major reason for this has been the recognition that interactions between mitochondria and calcium play fundamental roles in the regulation of cellular function under both normal and pathological conditions. The 13 articles in this issue review the key developments in this expanding area of research.

The ability of mitochondria to accumulate large amounts of calcium has been known for more than 50 years through the studies of such pioneers of mitochondrial bioenergetics as Albert Lehninger and Britton Chance. This calcium accumulation was found to occur at the expense of oxidative phosphorylation and to be driven by the mitochondrial membrane potential. Subsequently it was recognized that in addition this rapid influx mechanism mediated by a channel in the mitochondrial inner membrane there are also efflux mechanisms driven directly or indirectly through the pH gradient across the mitochondrial membrane. The relative activity of these two transporters sets the free concentration of calcium inside the mitochondria ($[Ca^{2+}]_m$). These transport mechanisms and their role and regulation are reviewed in this issue by Tom Gunter and Shey-Shing Sheu in their article. The early studies on mitochondrial calcium uptake employed calcium concentrations far higher than usually experienced by mitochondria in a healthy cell. Such studies led to the conclusion that a major role of mitochondrial calcium uptake was as a "fire extinguisher" to remove excess calcium from the cytosol. Indeed, work by David Nichols and discussed in his review, demonstrated that when mitochondria were exposed to sequential pulses of calcium they rapidly accumulated it, while the extramitochondrial $[Ca^{2+}]$ returned to the same "set point" after each pulse. At this "set point" the extramitochondrial $[Ca^{2+}]$ allows the influx pathway to operate at the same rate as the efflux pathways whose activities are working at $V_{max}$ rates because of the saturating matrix $[Ca^{2+}]$.

The view that the major role of mitochondrial calcium uptake is to prevent dangerous rises in cytosolic $[Ca^{2+}]$ was soon to be challenged by the discovery that several mitochondrial dehydrogenases are activated either directly (FAD-glycerol phosphate dehydrogenase, 2-oxoglutarate dehydrogenase and isocitrate dehydrogenase) or indirectly through dephosphorylation (pyruvate dehydrogenase) by submicromolar $[Ca^{2+}]$. These studies, pioneered by Dick Denton, Jim McCormack and Richard Hansford are reviewed in the article by Dick Denton. Their studies led them to propose that the primary role of mitochondrial calcium uptake under physiological conditions is to enable stimulation of respiration and oxidative phosphorylation in response to an increase in ATP demand. Through calcium regulation of the dehydrogenases this could without a change in ATP/ADP ratio and subsequent evidence from many laboratories has confirmed this to be the case. In this issue, the importance of this mechanism in regulating the bioenergetic function of the heart in response to increased workload is reviewed in the article by Bob Balaban. The article by Elinor Griffiths and Guy Rutter illustrates how the use of calcium- and ATP-sensitive probes targeted to mitochondria has confirmed the importance of this mechanism in a variety of cell types including isolated beating heart cells. The development of mitochondrial-targeted calcium-sensitive fluorescent and luminescent proteins, pioneered by the group of Tullio Pozzan, has played a key role in these studies and the article by Tullio Pozzan and Rüdiger Rudolf reviews this work. In particular, they describe how the technique can be used to monitor mitochondrial $[Ca^{2+}]$ in real time in tissues of live mice.

Not only can calcium regulate ATP production by mitochondria, but it can also influence mitochondrial motility such that the organelles are recruited to areas of the cell with high energetic demands. This is reviewed by Luca Pellegrini and colleagues who also discuss the role of calcium in regulating mitochondrial fission and fusion in cells under normal and pathological conditions.

Studies using targeted calcium-sensitive probes to measure calcium in different compartments of the cell have revealed that mitochondria do not simply respond to changes in cytosolic $[Ca^{2+}]$. Rather, it became apparent that they preferentially take up calcium released by the endoplasmic reticulum (ER) and sarcoplasmic reticulum (SR). This provides an intimate link between signal transduction pathways and mitochondrial $[Ca^{2+}]$ that enhances the response of mitochondria to match ATP production to ATP demand. This link is provided by the close association of the ER and SR with the mitochondria as reviewed in the article by Sarino Rizzuto and colleagues. Gyorgy Csordas and Gyorgy Hajnoczky also discuss this interaction in their article and describe how an interplay between calcium and reactive oxygen species (ROS) may play an important role. In addition to their role in allowing preferential mitochondrial calcium uptake, these interactions between SR/ER and mitochondria also provide a mechanism by which mitochondria can modulate calcium signaling within the cell and this is discussed by Alexei Tepikin and colleagues in their review. In addition, modulation of intracellular calcium signaling by mitochondria may also involve effects on the activity of plasma membrane calcium channels and transporters and this is discussed by Nic Demaurex and colleagues.

In addition to the physiological roles of the interactions between calcium on mitochondrial, excess calcium uptake can also disrupt mitochondrial function, especially when accompanied by oxidative stress, through the opening of the mitochondrial permeability transition pore (MPTP). Opening of the MPTP converts mitochondria from ATP producing to ATP consuming organelles and further activates ROS formation which, left unchecked, will lead to cell death. This death is primarily by necrosis when ATP depletion is severe, although the accompanying mitochondrial swelling and outer

0005-2728/$ – see front matter 
doi:10.1016/j.bbabio.2009.07.011

membrane rupture will also lead to cytochrome *c* release and the initiation of apoptosis if ATP levels are less compromised. The three articles by Andrew Halestrap, David Nicholls and John Lemasters review the molecular identity and regulation of the MPTP and its pathophysiological role in the heart, brain and liver. Their reviews describe how MPTP opening is now known to be the major cause of cell death under a variety of pathophysiological conditions including ischemia/reperfusion, neurodegenerative diseases and drug toxicity. They also indicate how pharmacological inhibition of the MPTP offers a promising therapeutic target for the treatment of such disease states.

Editing this issue has convinced me further that the interactions between calcium and mitochondria are fundamental to the life of the cell in health and disease. When mitochondria are performing their ancestral role as bioenergetic machines providing ATP to match demand, regulation by calcium provides a new level of sophistication that allows parallel stimulation of ATP synthesis with ATP demand. The interactions between the ER and the SR are key to the success of this regulatory mechanism since they allow preferential mitochondrial uptake of the calcium released from these stores during signaling events. It seems likely that over evolutionary history these interactions developed an additional use in shaping cytosolic calcium signals by dampening cytosolic calcium transients that accompany ER release. On top of this, close associations between mitochondria and plasma membranes enable further modulation of calcium signaling by rapidly removing calcium from beneath the plasma membrane.

One may think of these mitochondrial calcium interactions as reflecting the good side of the organelle, but like Dr. Jeckyll and Mr. Hyde, mitochondria possess two distinct personas. Under conditions of calcium overload, especially when accompanied by oxidative stress, opening of the MPTP causes mitochondria to embrace their darker side, and they become instruments of death. One of the remaining mysteries is why mitochondria should have evolved this dark side. What survival benefits does the MPTP have that would favor its selection in evolutionary history? Perhaps the involvement of calcium in both processes provides a clue. If calcium drives the bioenergetic functions of mitochondria harder to fulfil a greater energy demand it will also enhance ROS production. With time this will damage mitochondria, including their DNA, and one role of the MPTP might be to remove such worn out mitochondria on an individual basis. This could be achieved without bioenergetic compromise of the cell. However, when an overwhelming insult occurs, the loss of mitochondria becomes sufficient to kill the cell as occurs in reperfusion injury such as following a stroke or coronary thrombosis. This is probably not a common event in past evolutionary history but is becoming a major problem in affluent western society.

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Andrew Halestrap is Professor of Biochemistry at the University of Bristol. He studied Natural Sciences at Cambridge, specialising in Biochemistry, before moving to the Department of Biochemistry at the University of Bristol to study the regulation of fat cell metabolism under the supervision of Richard (Dick) Denton. He was awarded his Ph.D. in 1974 and has stayed in Bristol ever since, becoming full professor in 1996. During his doctoral studies he discovered specific inhibitors of the plasma membrane and mitochondrial monocarboxylate (lactate and pyruvate) transporters and he has continued to work on the structure, function and regulation of these transporters ever since. However, his work on the mitochondrial pyruvate carrier led him to investigate the regulation of liver mitochondrial function by hormones and it was these studies that initiated an interest in the regulation of mitochondrial function by calcium. During the 1980s Dr. Halestrap focussed on the hormonal regulation of liver mitochondrial metabolism mediated by a calcium-induced increase in matrix volume. However, by 1990 it was the pathological effects of calcium to cause massive mitochondrial swelling through the opening of the mitochondrial permeability transition pore (MPTP) that became the major focus of his work. He has made seminal contributions to the molecular mechanism of the MPTP and its critical role in reperfusion injury of the heart and brain. Dr. Halestrap was elected a Fellow of the Academy of Medical Sciences in 2008 and has been invited to give The Keilin Memorial Lecture of the Biochemical society in 2010.